

REMARKS

Upon amendment, Claims 1-2, 4-13, 15-18, 48, 49, 51, 52, 56-60, 65, 66, 70-73, 77, 79, 83-88, 90, 91, 93, 99-102 are pending in this application, of which Claims 4-13, 15-18, 52, 58-60, 66, 70-72, 84-87, 90, 91, and 93 are presently withdrawn. Claims 23, 24, 37, 41, 44, and 50 are cancelled herein without prejudice. Claims 1 and 65 are amended to recite that the triarylphosphonium portion of the labeling reagent is selected from the group consisting of unsubstituted naphthyldiphenylphosphine, dinaphthylphenylphosphine, trinaphthylphosphine, 9-anthryldiphenylphosphine, 9-anthryldinaphthylphosphine, diphenylpyrenylphosphine, dinaphthylpyrenylphosphine. Support for this amendment can be found throughout the specification as originally filed, for example in Claim 37.

Claims 101 and 102 are new and are directed to methods in which the biological sample are not further cleaned-up or desalted after labeling. Support for these claims can be found throughout the specification, specifically at Page 4, lines 29-30; and page 53, lines 3-6.

Amendment and cancellation of claims herein were done solely to expedite prosecution of the application and should not be construed as acquiescence to any rejections set forth in the pending office action or any previous Office Action. Applicants respectfully reserve the right to pursue any non-elected, cancelled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the objections to and the rejections of this application in view of the amendments and remarks herewith, are respectfully requested, as Applicants submit that the application is in condition for allowance.

Claim Objections

Claim 23 stands objected to as failing to further limit the subject matter of a previous claim. Applicants note that Claim 23 has been canceled without prejudice and thus the objection to Claim 23 is now moot.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 2, 23, 37, 41, 44, 46, 51, 56, 57, 65, 73, 77, 79, 83, 88, and 89 are rejected under 35 U.S.C. 103(a) as unpatentable in view of Huang *et al* (*Analytical Biochemistry*, 1999, IDS) (“Huang”).

The Office Action alleges that Huang teaches a method of preparing a sample for mass spectrometry analysis comprising “reacting the analyte with a triaryl phosphonium labeling reagent (Tris(trimethoxyphenyl)phosphonium(TMPP) reagents) having a reactive group.” Indeed, Huang only teaches the use of Tris(2,4,6-trimethoxyphenyl)phosphonium reagents.

Claims 1, 41, 50, 88, 99 and 100 are rejected under 35 U.S.C. 103(a) as unpatentable in view of Leavens *et al* (*Rapid Communications in Mass Spectrometry*, 2002, IDS) (“Leavens”).

The Office Action alleges that Leavens teaches a method of preparing a sample for mass spectrometry analysis comprising “reacting the analyte with a triarylphosphonium labeling reagent (TMPP-reagents) having a reactive group.” Indeed, Leavens only teaches the use of TMPP reagents.

As amended, Claims 1 and 65, from which all other claims depend, have been amended to recite that the triarylphosphonium portion of the labeling reagent is selected from the group consisting of unsubstituted naphthyldiphenylphosphine, dinaphthylphenylphosphine, trinaphthylphosphine, 9-anthryldiphenylphosphine, 9-anthryldinaphthylphosphine, diphenylpyrenylphosphine, dinaphthylpyrenylphosphine (as in, for example, claim 37). As both Huang and Leavens are limited to the use of Tris(2,4,6-trimethoxyphenyl)phosphonium (TMPP) reagents, *i.e. triarylphosphonium with substituted aryl groups wherein said substituents are methoxy substituents*, Applicants respectfully assert that neither Huang nor Leavens renders the claimed invention obvious.

Specifically, Applicants respectfully submit that one of ordinary skill in the art would expect significantly different chemical properties (steric, electrochemical, pharmacological, etc) between labeling reagents bearing three electron-donating methoxy substituents bound to a phosphine-bound phenyl group and labeling reagents having between 1 and 3 unsubstituted, phosphine-bound bulky aromatic groups.

Indeed, one of ordinary skill in the art would recognize that the electron-donation of the methoxy groups would likely make the TMPP reagents stronger Lewis bases than the unsubstituted, bulky groups of the compounds of the instant claims. That is, their ability to donate electrons and thereby associate with the analyte would be expected to be stronger. Furthermore, the steric bulk of the compounds of the instant claims would be expected to be a hindrance in the reactivity of these reagents with the analyte.

As such, applicants contend that one of ordinary skill in the art would have had no motivation to modify the TMPP reagents of Huang or Leavens to arrive at the labeling reagents of the instant claims. Furthermore, even if one of ordinary skill in the art were to remove the electron-donating groups from the TMPP reagent, one of ordinary skill in the art would have had no reasonable expectation of success in further modifying the reagents to include the bulky aromatic groups of the instant claims.

With regards to Claims 88, 99, and 100, the Examiner states that “while Huang does not specifically teach that the sample is a biological tissue, it is well known that proteins can be obtained from biological tissue.” Similarly, the Examiner states that “Leavens teaches analyzing amines and carboxylic acid compounds” but while Leavens “does not teach that the sample , the Examiner states that while “Leavens does not specifically teach that sample is a biological tissue. It is well known that amines can be obtained from biological tissue.”

Applicants respectfully reassert that **Claims 88, 99, and 100 do not relate to the use of a protein or an amine from a biological tissue as a sample, but instead Claims 88, 99, and 100 relate to the use of a *biological tissue as the sample itself*.** Although Applicants agree that

proteins and amines can often be obtained from a biological tissue, Applicants respectfully disagree that obtaining a protein or an amine from a biological tissue as a sample for mass spectrometry analysis and using the biological tissue itself as a sample for mass spectrometry analysis would be seen as obvious variations.

Indeed, a biological tissue may comprise other types of molecules (small molecules, non-proteinaceous compounds) which can be analyzed by Mass Spectrometry and which may be of importance to one skilled in the art. As such, Applicants respectfully contend that one of ordinary skill in the art, upon reading of the use of proteins as a sample in Huang or amines as a sample in Leavens would have had **no motivation and no reasonable expectation of success in using a *biological tissue itself* as a sample** for Mass Spectrometry.

Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the remarks made herein, Applicants submit that the application is in condition for allowance. Accordingly, Applicants respectfully request entry of the amendments and remarks presented herein, favorable reconsideration of the application and prompt issuance of a Notice of Allowance.. If a telephone conference with Applicants' representative would be helpful in expediting prosecution of the application, Applicants invite the Examiner to contact the undersigned at the telephone number indicated below.

Applicants believe that no additional fees are required in connection with this paper. Nevertheless, Applicants authorize the Director to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 04-1105, under Order No. 64254(49991).

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Respectfully submitted,

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